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<b>(21) International Application Number:</b> PCT/DK86/00050 <b>(22) International Filing Date:</b> 7 May 1986 (07.05.86) <b>(31) Priority Application Number:</b> 2092/85 <b>(32) Priority Date:</b> 10 May 1985 (10.05.85) <b>(33) Priority Country:</b> DK  <b>(71) Applicant (for all designated States except US):</b> FERTIN LABORATORIES A/S (DANSK TYGGEGUMMI-FABRIK A/S) [DK/DK]; P.O. Box 299, DK-7100 Vejle (DK). <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only) :</b> LÜTZEN, Claude, Erik [DK/DK]; 9, Hans Egedesvej, DK-7100 Vejle (DK). <b>(74) Agent:</b> CHAS. HUDE; 33, H.C. Andersens Boulevard, DK-1553 Copenhagen V (DK).		<b>(81) Designated States:</b> AU, BE (European patent), CH (European patent), DE (European patent), FR (European patent), IT (European patent), JP, NL (European patent), NO, SE (European patent), US.  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> A SOLID ORAL ANTICARIOGENIC COMPOSITION  <b>(57) Abstract</b>  A solid, oral, anticariogenic composition in the form of a chewing gum or a lozenge and beyond the conventional chewing gum or lozenge ingredients containing as dental plaque acid-neutralizing ingredient urea in an amount from 0.5% by weight to 80% by weight, based on the total weight of the composition, an optional coating not being taken into account. The composition is used for reducing the risks of dental caries subsequently to eating and drinking as it causes a neutralization of the plaque acids.		

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Title: A Solid Oral Anticariogenic Composition.

Technical Field

The invention relates to a solid oral anticariogenic composition in the form of chewing gums or lozenges. More particularly, the present invention relates to an anticariogenic product to be used for neutralizing the acid produced in dental plaque subsequent to eating or drinking.

Background Art

The prior art has long sought a means to control the cariogenic effect of comestibles and sweetened beverages and the like.

Several ways exist of protecting the teeth against bacterial attacks. In order to explain the latter please find below a short description of the caries theory accepted today.

The mouth is a biological environment usually being well-balanced. When the food has entered the mouth it is divided into fine particles by the teeth at the same time as it is softened by the saliva. The biological environment includes furthermore the microflora existing in the mouth.

The above microflora includes bacteria, especially a certain group of bacteria, viz. the facultative anaerobes, capable of decomposing carbohydrates in the absence of oxygen into organic acids, especially lactic acid. The acid attacks the dental enamel and the underlying dentine which causes a demineralisation. A reaction implies that a thin layer of the enamel is dissolved. Repeated reactions may cause caries or a "hole in the tooth". The critical pH-value of demineralisation is 5.5. Below this value the enamel and the underlying dentine are dissolved. Above a

pH of 5.5 the enamel and the dentine are remineralised.

The remineralisation comprises a regeneration of dentine and enamel by components from the saliva. The demineralisation must not, however, be too advanced if a successful remineralisation is to be obtained.

(1) A demineralisation of the teeth requires the presence in the mouth of facultative anaerobic bacteria, carbohydrate, water, anaerobic conditions, as well as the correct temperature. If these conditions do not exist the process does not take place.

Thus different ways of preventing formation of caries exist.

It is possible to avoid anaerobic conditions by removing plaque (tooth-cleaning for instance by means of a tooth brush, dental floss, toothpicks or by polishing). The resistance of the enamel to acid attacks can be increased for instance by a fluorine treatment (brushing the teeth by means of a fluorine-containing toothpaste, rinsing or swabbing with a fluorine-containing agent). The facultative anaerobic bacteria can be inactivated for instance by intervening in the glycolysis.

It is possible to ensure that the acid produced is neutralized as quickly as possible. Finally the production of saliva can be stimulated in order to improve the cleaning of the teeth, "the defence mechanism of nature itself". During the latest decades much has been done for teaching the population dental care, especially eating less sweets and brushing teeth by means of fluorine-containing toothpaste at least twice a day. Furthermore fluorine has in certain areas been added to the drinking water. In spite of these measures caries still arises. The fluorine toothpaste reduces the caries frequency by 30-40% provided the

teeth are carefully brushed twice a day.

The largest caries risk group is children with newly erupted permanent teeth. Especially many children do not brush their teeth as regularly as they ought to. West  
5 German investigations have shown that for instance in 1970/ 1971 1% of the children never brushed their teeth, and 10% of the children brushed their teeth irregularly. Among 2/3 of the teeth-brushing children each brushing took less than 1 minute. Furthermore many children often  
10 eat sugar-sweetened products, which happens frequently between the regular meals and under circumstances making it difficult to brush the teeth afterwards.

Under particular circumstances where an actual brushing of the teeth is difficult or impossible, such as after  
15 lunch, after snacks, and in connection with long meetings and when travelling, adults can also have a need for an easy possibility of cleaning their teeth.

Thus an essential need exists for a means applicable in an easy and practical manner as a suitable supplement to  
20 the daily tooth-brushing. Attempts at fulfilling the above need are already known.

As a result sugar-free chewing gum exists which has been sweetened especially by sorbitol as the sorbitol is not decomposed into organic acids under normal conditions and  
25 thus does not cause a risk of formation of caries but in the usual way increases the secretion of saliva. The advantage of such a product is that it is harmless to the teeth, but the chewing of sugar-free chewing gum of this type does not involve an active caries prophylaxis.

30 Beyond being an ingredient in toothpaste the fluorine has also been used in mouthwash, lozenges, and chewing gums.

Especially the chewing gum is suitable for being brought along in the pocket or the bag. However, as previously mentioned the fluorine can only increase the resistance of the enamel against acid attacks to a certain degree.  
5 Furthermore the toxicological aspects in connection with intake of fluorine must be considered.

Attempts have also been made of using various alkaline substances for the neutralization of acid, cf. e.g. Norwegian Patent No. 46,152 from 1929 concerning a chewing  
10 gum composition containing magnesia oxide, but due to the taste the products containing such substances were never a success.

JADA 96:651-655, 1978 describes a triennial clinical study of chewing gum containing trimethaphosphate. The results  
15 were not satisfactory.

G.T. Grove and C.J. Grove 1934: "The biological aspect of dental caries". Dent. Cosmos 76: 1029 and C.J. Grove and C.T. Grove 1935: "Chemical study of human saliva indicating that ammonia is an immunizing factor in dental  
20 caries." J. Amer.dent. Ass. 22: 247 believed that ammonia - which they assumed derived from the urea of the saliva - was responsible for the caries immunity of human beings. They imagined that ammonia acted by reducing the formation of plaque. Various other scientists were, however, in-  
25 capable of proving this relationship between a tendency to form caries and the concentration of ammonia in the saliva (J. White and R.W. Bunting, 1935: "An investigation into the possible relationship of ammonia in the saliva to dental caries."

30 J. Amer. dent. Ass. 22: 468, G.E. Youngburg, 1935-36: "Salivary ammonia and its relation to dental caries." J. dent. Res. 15: 247. M. Karshan, 1936: "Factors in human saliva correlated with the presence and activity of dental

caries." J. dent. Res. 15: 383-293).

I. Kleinberg and G.N. Jenkins 1964: "The pH of dental plaques in different areas of the mouth before and after meals and their relationship to the pH and rate of flow of resting saliva." In Archs. oral Biol. 9: 493-516, it was shown that in vivo plaque pHs are above the saliva pH and the hypothesis was set forth that the above is due to the fact that plaque bacterial ureases convert saliva urea into ammonia. This theory was supported by T.M. Hassel 1972: "The effect of acetohydroxamic acid on interdental pH assessed with radio telemetry." Helv. odont. Acta 16: 27-31, where a pH drop in mouthwater and interdental plaque upon use of urease inhibitor were shown by in vivo studies.

R.M. Stephan 1940: "Two factors of possible importance in relation to the etiology and treatment of dental caries and other dental diseases." Science 92: 578-579, was of the opinion that ammonia from urea in the saliva would cause a neutralization of part of the plaque acids produced after intake of carbohydrate-containing food. Furthermore he described that the pH in plaque on tooth surfaces and in cavities rose to 8.5 upon rinsing with a concentrated carbamide solution (synthetic urea).

Clinical tests with dentifrices containing urea and ammonium salts gave contradictory results and interest waned rapidly (for a review see B. Regolati 1971: "Ammonia and urea in oral pathophysiology - a literature review". Helv. odont. Acta 15: suppl. 7, pp 139-146).

In a reprint of Sveriges Tandläkarförbunds Tidning No. 8, 1963, G. Frostell and I. Erickson have described the addition of urea to carbohydrate-containing food such as sweets, chocolates, marmelades, confectionaries as a possible means for controlling caries. They concluded that an elimination or reduction, if any, of the caries-pro-

ducing effect of carbohydrate-containing food could possibly be obtained if the articles of food contain urea. Later tests carried out by some of the most recognized scientists within the anticariogenic field gave, however, 5 the conclusion that urea is inactive as far as a reduction of plaque and caries is concerned, cf. A. R. Firestone et al., Caries Res. 16: 112-117, 1982. While urea is stated to be inactive, urea hydrogen peroxide and hydrogen peroxide are on the contrary stated to be very effective for 10 reducing plaque accumulation and the frequency of caries. US patent specification No. 4,302,441, Hans R. Mühlemann et al., states that solid oral glycerol-free preparations containing active urea hydrogen peroxide are effective for counteracting acids formed by fermentable carbohydrates 15 in dental plaque. Both above publications are about 20 years later than the previously mentioned reprint and both reveal a direct prejudice against urea per se being applicable for preparing an efficient anticariogenic composition. Unlike the latter, urea hydrogen peroxide is 20 considered applicable for formulating efficient, stable oral preparations as the above late tests all ascribe the anticariogenic effect to the hydrogen peroxide part.

At present two dentifrice chewing gum products containing solid urea hydrogen peroxide are on the market in Denmark, viz. V6<sup>+</sup>® produced by Fertin Laboratories A/S and 25 Caroxin® produced by Ferrosan, the latter product having been on the market since 1927, and it appears from the Danish catalogue of medicines that H<sub>2</sub>O<sub>2</sub> is considered being the active ingredient in both said products. Tests have 30 proved that these products are active by intake after intermediary meals since at quickly chewing they cause an increase of the plaque pH to a level above the previously mentioned critical pH of 5.5 for the demineralisation. In a Directive 76/768 concerning cosmetics the EEC commission 35 has, however, prohibited the addition of hydrogen peroxide to compositions for internal use.



GB Patent No. 673,670 discloses dentrifices for neutralizing the acid in dental plaque including chewing gums containing urea and urease. Such chewing gums containing urease must be prepared and stored under strictly moisture-free conditions and the processing temperature must be kept below 50-60°C to avoid denaturation leading to inactivation of the urease.

Water must be present by the conventional process for the preparation of chewing gum and during the mixing process the temperature rises to 60°C and locally to 80°, and the chewing gum proposed in GB Patent No. 673,670 can consequently not be prepared by the conventional process without decomposition of the urea and urease.

The preparation of said proposed urease-containing chewing gum product in moisture-free form and using a mixing temperature below 50°C would be difficult and the resulting product would certainly have unsatisfactory organoleptic properties. During the entire preparation the product must be surrounded by a dry atmosphere corresponding to the necessary conditions for preparing effervescent tablets. It is very expensive to establish such conditions and the rooms having the necessary low humidity are unpleasant for the production staff.

Furthermore, it is necessary to provide for cooling during the mixing and extrusion process to ensure that the temperature does not exceed 50°C in order to avoid denaturation and decomposition of the urease. Such cold mixing temperatures make it very difficult and expensive to obtain a homogeneous product.

Finally, a product containing both urea and urease will require a special moisture-proof package, which should probably also contain a desiccant, e.g. in the form of a

tablet.

It has now turned out surprisingly that unlike the other bases present in the saliva, urea can be used as the only active ingredient of a solid oral anticariogenic composition in the form of chewing gums or lozenges. Such a composition solves the above problems described concerning an easy access to a supplementary dental care without risks for the health and without the bad taste arising when using other bases.

10 Furthermore the composition fulfils the demand given by the Directive 76/768 concerning cosmetics of the EEC commission for a product replacing the previous hydrogen peroxide-containing products.

Finally, the products according to the invention may be produced without special measures under conventional conditions by means of conventional equipment for producing chewing and lozenges, respectively. This makes the production more inexpensive and less complicated than the production of e.g. the above urease containing products.

## 20 Description of the Invention

The object of the present invention is to provide a novel solid oral anticariogenic composition in the form of a chewing gum or a lozenge which overcomes the above disadvantages of the prior art.

25 The foregoing and other objects, advantages, and features of the invention are achieved by a solid oral anti cariogenic composition in the form of a chewing gum or a lozenge to be used for neutralizing acid in dental plaque subsequent to eating and drinking, which composition is characterised in that beyond the conventional chewing gum or lozenge ingredients the composition comprises as active

ingredient urea or pharmacologically acceptable substances capable of releasing urea under the conditions prevailing in the oral cavity in an amount from 0.05% by weight to 80% by weight, calculated as urea, based on the total weight of the composition, an optional coating not being taken into account.

The composition according to the invention is thus remarkable for not containing hydrogen peroxide and consequently it does not conflict with the previously mentioned EEC Directive 76/768. Furthermore the composition is biologically acceptable and non-toxic (cf. the indication in the American GRAS list) the active ingredient being a natural component of the saliva. The latter also implies that the active component has an acceptable taste at oral intake in the indicated doses. The composition according to the invention increases the period of contact between urea and the teeth resulting in an improved anti-cariogenic effect.

Through intake of the composition subsequent to eating or drinking the caries risk is essentially reduced which has been proved through in vivo tests unambiguously proving an increased pH upon chewing the composition for a certain period after the eating or drinking. The circumstance that the composition is a product to be chewed ensures firstly that the active component of the product is distributed in the mouth and reaches the sites where the anticariogenic effect is needed and where it is often difficult to clean the teeth efficiently by tooth brushing, and secondly that the stay of the product in the mouth suffices for providing the necessary increase of the pH. Thirdly the form of the composition as a chewable product causes a saliva secretion-improving effect, and a high saliva secretion is of decisive importance to the anti-cariogenic effect.

The effect of the composition according to the invention has been tested using telemetric plaque pH measurements. The connection between caries and plaque pH is well-known, i.a. as described by T. Imfeld in "Identification of low  
5 caries risk dietary components, Monographs in Oral Science", vol. 11, p. 83-85, Myers, H.M. Editor, Karger, Basel, 1983, in which he reports that foodstuffs which in the plaque pH measurement system show no or only low acid production have no caries-increasing effect tested on  
10 rats and humans. On the other hand it has been shown that any foodstuff which causes caries in tests on animals and humans is also acid producing in interdental telemetric plaque pH-tests. Thus, it is generally accepted that telemetric plaque pH measurements are a significant indication  
15 of the possibility of caries development, and that a plaque acid neutralizing means is an effective anticariogenic means.

The composition according to the invention must be formulated as a chewing gum or a lozenge in order to ensure  
20 a sufficiently long stay thereof in the mouth, preferably for at least 10 minutes. In this manner the possibility of an efficient neutralization of the plaque acid produced by eating or drinking is ensured.

When a composition according to the invention is chewed  
25 or sucked immediately after eating or drinking, the desired acid-neutralizing effect in the oral cavity is obtained, and especially on sites with heavy plaque.

By using a composition according to the invention the normally occurring pH drop to a value below 5.5 usually re-  
30 maining for about 30-40 minutes is eliminated. By using the composition according to the invention after each eating and drinking, and also after an additional intake within the above already critical 30-40 minutes, the further extension of the demineralisation phase is avoided.

It is a fact that the longer the demineralisation phase lasts the greater is the probability of caries.

By using the composition according to the invention in the manner described a momentaneous neutralization of the acid is ensured after eating or drinking, and the plaque pH can be kept above 5.5. The possibility of intake of a composition according to the invention implies furthermore as an additional, favourable side effect that the craving for another intake of carbohydrate such as snacks, sweets and ice no longer applies or at least is postponed.

It is assumed that the effect of the composition according to the invention is based on a co-operation of several processes. By chewing or sucking the composition the secretion of saliva and consequently the flow of saliva is multiplied in such a manner that both a dilution and a rinsing of the plaque environment take place. Furthermore the natural buffer system of the saliva implies that a certain neutralization of present acid occurs. An efficient neutralization of acid in order to maintain a pH above 5.5 is obtained by the urea content of the composition as the composition according to the invention is formulated in such a manner that its urea content is released as quickly as possible. The released urea is momentarily converted by urease into ammonium carbonate and further into ammonia and carbon dioxide. The ammonia reacts instantaneously with any present acid and the gradually produced acid whereby the plaque pH is increased from a demineralisation-causing level below 5.5 to the remineralisation level above 5.5 where the pH is kept through continued chewing and/or sucking of the composition of the invention used.

In practice the release of urea into the saliva which functions as a vehicle can commence immediately after termination of a meal as the person in question can take one

or more pieces of chewing gum or one or more lozenges without involving practical problems no matter where the person is. Contrary to the latter it is seldomly possible for a person to have his teeth brushed or his mouth rinsed  
5 with a suitable product. The immediate release of urea by using a composition according to the invention implies that it is possible to avoid the high concentration of acid usually being the major cause of caries.

The physical embodiment of the composition as a chewing  
10 gum or a lozenge implies that the carrier of the composition always alters its position in the mouth via the saliva, and thereby ensures an efficient distribution of the acidneutralizing urea even to less accessible places such as between the teeth, where debris according to experience  
15 cause a particularly high production of acid and consequently require a particularly high acid-neutralizing effect.

As previously explained it is not only important to obtain a momentaneous neutralization of acid but also to ensure  
20 that the pH does not drop below 5.5. At intake of most food and beverages a deposit of a certain portion of carbohydrate in plaque occurs. If the plaque or the carbohydrate is not removed not only an instantaneous neutralization of acid is needed but also a possibility of neutralizing  
25 the acid currently produced on account of remaining carbohydrate residues involving a risk of a drop of the pH to below 5.5.

The composition according to the invention is formulated so that the urea content thereof in combination with the  
30 puffer released by the saliva compensates to a high degree for the amount of acid present in plaque after intake of carbohydrate.

#### Description of the Preferred Embodiments of the Invention

A preferred composition according to the invention contains in each dosage unit at least 5 mg of urea. In practice the intake of urea should always amount to at least 5 mg in order to ensure a sufficient effect. The necessary 5 mg can, of course, always be taken in the form of several pieces of chewing gum at a time or several lozenges or both chewing gum and lozenge. The composition according to the invention contains preferably from 0.2% by weight to 25% by weight of urea based on the weight of the total composition. In practice a content within this range gave the best results. A urea content exceeding 80% by weight is inapplicable in practice. In order to utilize the favourable effects of the composition according to the invention efficiently it is necessary to chew or suck the composition according to the invention immediately after the eating and drinking for a period sufficient for releasing the active urea ingredient in an amount sufficing for the neutralization of plaque acid. By a sufficient period is usually meant a period of at least 30 sec., preferably 10 min. There are no limits as to how long the composition can be used, but in practice it is, of course, limited how long the active chewing or sucking process is desired to continue.

The keeping of the composition in the mouth for a long time ensures in combination with the above stimulation of the secretion of saliva the advantage that the tendency to desire new snacks, sweets, cakes, ice etc. is reduced whereby the period in which the plaque pH is kept on the remineralisation level is made as long as possible.

It must be expected that most people will feel attracted to the comfortable possibility of improving the oral hygiene at the same time as they obtain a caries-reducing effect merely by taking a piece of chewing gum or a lozenge for instance after each meal. In this connection it should be mentioned that the composition according to the

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invention can be made extra attractive by containing various additives such as e.g. flavour additives or sweeteners. All the usual additives for chewing gums and lozenges, of course, can be used.

- 5 A chewing gum according to the invention may advantageously have the following composition:

	Gum base	15	-	50% by weight
	Sweetener	40	-	80% by weight
	Flavour	0.5	-	4% by weight
10	Urea	0.8	-	4% by weight
	Water, Colour, etc.	0	-	5% by weight

an optional coating not being taken into account.

- 15 A lozenge according to the invention may advantageously have the following composition:

	Sweetener	80	-	99% by weight
	Flavour	0	-	4% by weight
	Lubricant	0	-	4% by weight
	Urea	0.6	-	4% by weight
20	Water, Colour, etc.	0	-	4% by weight.

When the composition according to the invention is formulated as a chewing gum, the form thereof may be chosen among any of the known types of chewing gum such as chewing  
25 gum pieces optionally coated, as well as chewing gum sticks or chewing gum of an arbitrarily desired different shape depending on the intended use. The chewing gum may be of any quality, including bubble gum. No limits exist as to the chewing gum bases applicable in the chewing gum accord-  
30 ing to the invention. Usual types of chewing gum bases such as for instance those available from L.A. Dreyfus



Company or Cafosa Gum A/S are generally suitable, but specially manufactured formulations can also be used. The formulation depends on the desired type of chewing gum as described above or on the desired type of structure. Suitable raw materials for gum bases include the substances according to U.S. Chewing Gum Base Regulations - Code of Federal Regulations, Title 21, section 172.615.

The weight of the gum base lies in the range of from about 15 to about 90%, preferably from 30 to 40% by weight based on the weight of the total composition an optional coating not being taken into account.

The amount of further auxiliaries in chewing gum is usually from about 10 to about 85% by weight.

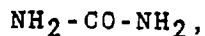
As examples of suitable flavours the following can be mentioned: Peppermint, wintergreen, eucalyptus, spearmint, fruit flavours and any other flavour applicable in confectionery and toothpaste, including mixtures of flavours.

As sweetening ingredient in the composition according to the invention the use of sweeteners not detrimental to the teeth is recommended. Examples thereof are sorbitol, xylitol, Lycasin<sup>®</sup>, glycerol, aspartame, saccharine, cyclamate as well as mixtures thereof or mixtures thereof with other suitable sweeteners.

The composition according to the invention comprises preferably powdered sorbitol and/or xylitol in an amount from about 40 to about 80% by weight, preferably from 50 to 70% by weight.

A 70% by weight aqueous solution of sorbitol, Lycasin<sup>®</sup> and/or glycerol can advantageously be present in an amount from 0 to 30% by weight, preferably from about 0 to 15% by weight.

The active component urea has the formula



and is a white crystalline solid with a melting point from 132 to 133°C. It is easily soluble in water, slightly  
5 soluble in ethanol and methanol, and substantially insoluble in ether and chloroform. The quality of the urea used should comply with the valid pharmacopees e.g. Pharm. Nord. 1963 - USP XXI or BP 80.

Beyond urea the composition according to the invention  
10 comprises also pharmacologically acceptable substances capable of releasing urea under the conditions prevailing in the mouth. Examples thereof are: Salts and addition compounds between urea and inorganic compounds such as magnesium sulphate, calcium phosphate, sodium chloride,  
15 etc.

The urea content of the composition according to the invention varies between 0.05% by weight and 80% by weight, preferably between 0.2% by weight and 25% by weight. If  
20 the composition contains a very small amount of urea it is necessary to take a greater amount of the composition as care should always be taken that the intaken amount of urea is sufficient for neutralizing the amount of plaque acid being present. This amount is usually at least 5 mg of urea.

25 The weight of a dosage unit of the composition according to the invention lies usually in the range of from about 0.5 g to about 20.0 g. The following Table indicates preferred ranges of various types of the product:

30	Chewing gums without a coating	750 - 3500 mg
	Chewing gum tablets with a sugar	

	coating	1200 - 6000 mg
	Chewing gum sticks	1.5 - 5.0 g
	Bubble gum	1.0 - 7.5 g
	Pressed lozenges	0.5 - 3.0 g
5	Cast lozenges	0.5 - 3.0 g

Apart from the fact that the lozenges according to the invention must contain lubricant and, of course, not chewing gum base, the suitable ingredients of lozenges correspond substantially to those described in connection  
10 with chewing gum.

The lozenges may, of course, contain any such additives usual for lozenges.

The invention will be further illustrated by means of the following examples of compositions of anticariogenic com-  
15 positions for oral administration in the form of chewing gums or lozenges.

#### Examples

##### Example 1

A non-coated chewing gum of the following composition:

20	<u>Ingredients</u>	<u>% by weight</u>
	Chewing gum base	42.0
	Xylitol powder	54.5
	Wintergreen flavour	2.25
	Urea	1.25

25 Of 80 g of the above composition 100 pieces of chewing gum were produced, each piece containing 10 mg of urea.

##### Example 2

A non-coated chewing gum of the following composition:

	<u>Ingredients</u>	<u>% by weight</u>
	Chewing gum base	35.5
	Sorbitol powder	51.5
5	Lycasine®	10.0
	Spearmint flavour	2.0
	Urea	1.5

Of 100 g of the above composition 100 pieces of chewing gum were produced, each piece containing 15 mg of urea.

10 Example 3

A non-coated chewing gum of the following composition:

	<u>Ingredients</u>	<u>% by weight</u>
	Chewing gum base	37.5
	Sorbitol powder	53.0
15	Glycerol	5.0
	Peppermint flavour	2.0
	Urea	2.5

Of 80 g of the above composition 100 pieces of chewing gum were produced, each piece containing 20 mg of urea.

20 Example 4

	<u>Ingredients</u>	<u>% by weight</u>
	Chewing gum base	40.0
	Xylitol	52.5
	Glycerol	3.0
25	Eucalyptus flavour	2.5
	Urea	2.0

Of 100 g of the above composition 100 pieces of chewing

gum were produced, each piece containing 20 mg of urea.

Example 5

	<u>Ingredients</u>	<u>% by weight</u>
	Chewing gum base	35.5
5	Sorbitol powder	44.5
	Sorbitol 70%	15.0
	Spearmint	2.0
	Urea	3.0

Of 100 g of the above composition 100 pieces of chewing gum were produced, each piece containing 30 mg of urea.

Example 6

	<u>Ingredients</u>	<u>% by weight</u>
	Chewing gum base	31.0
	Sorbitol powder	52.0
15	Lycasine®	15.0
	Fruit flavour	1.0
	Urea	1.0

Of 300 g of the above composition 100 pieces of chewing gum were produced, each piece containing 30 mg of urea.

20 Example 7

In order to ensure the proper taste, appearance, protection of the content as well as the packaging system the chewing gum tablets prepared according to the Examples 1-6 are coated with a real coating (dragée layer) and/or a thin surface layer by polishing or application of a film according to A, B or C:

A: Sorbitol as a 70% solution

B: Xylitol 70.0%

20

Water 30.0%  
C: Carnauba wax 25 g  
Bees' wax 25 g

optionally admixed colour, pigment, binder and/or additional water.

The surface layer was applied by means of a conventional dragée vessel until the desired weight per piece was obtained.

#### Examples 8

10 Bubble gum of the following composition was prepared:

	<u>Ingredients</u>	<u>% by weight</u>
	Chewing gum base	20.0
	Sorbitol powder	68.2
	Sorbitol 70%	10.0
15	Flavour	0.8
	Urea	1.0

Of 500 g of the above composition 100 pieces of bubble gum were produced, each piece containing 50 mg of urea.

#### Example 9

20 Chewing gum sticks of the following composition were prepared:

	<u>Ingredients</u>	<u>% by weight</u>
	Chewing gum base	25.0
	Sorbitol powder	64.0
25	Lycasine®	10.0
	Flavour	1.0
	Urea	1.0

Of 300 g of the above composition 100 chewing gum sticks

were prepared, each stick containing 30 mg of urea.

Example 10

Lozenges of the following composition were prepared by compressing:

5	<u>Ingredients</u>	<u>% by weight</u>
	Sorbitol powder	96.5
	Peppermint flavour	0.5
	Magnesium stearate	1.0
	Urea	2.0

10 The ingredients were mixed and tabletted by means of a conventional tableting machine.

Of 100 g of the composition 100 tablets were prepared, each tablet containing 20 mg of urea.

Example 11

15 Lozenges of the following composition were cast:

	<u>Ingredients</u>	<u>% by weight</u>
	Gum arabicum	35.0
	Sorbitol	62.7
	Peppermint flavour	0.3
20	Urea	2.0

The ingredients were mixed and cast into lozenges of about 1.5 g, each lozenge containing 20 mg of urea.

Example 12

Chewing gum pieces of the following composition were 25 prepared:

	<u>Ingredients</u>	<u>% by weight</u>
	Chewing gum base	37.5
	Sorbitol powder	51.5
	Glycerol	5.0
5	Peppermint flavour	2.0
	Urea calcium sulphate	
	addition compound $4(\text{CH}_4\text{N}_2\text{O})\cdot\text{CaSO}_4$	4.0

Of 80 g of the above composition 100 pieces of chewing gum were prepared, each piece containing 28 mg of 4  
 10  $(\text{CH}_4\text{N}_2\text{O})\cdot\text{CaSO}_4$  and being capable of releasing 20 mg of urea.

In the Examples 1-11 one or more alternative pharmacologically acceptable substances capable of releasing urea under the conditions prevailing in the oral cavity including e.g. the above mentioned addition compound may substitute the urea. In case of such substitution, the amount of urea used in the composition in question should, of course, be substituted an amount of the urea releasing substance which is able to release the equivalent amount of urea.

20 Further examples of substances that may be used are

$6(\text{CH}_4\text{N}_2\text{O})\cdot\text{MgSO}_4\cdot 2\text{H}_2\text{O}$  and  $\text{CH}_4\text{N}_2\text{O}\cdot\text{NaCl}\cdot\text{H}_2\text{O}$ .

Examples of equivalent amounts are:

$6(\text{CH}_4\text{N}_2\text{O})\cdot\text{MgSO}_4\cdot 2\text{H}_2\text{O}$	1.4 times the indicated amount of urea
$4(\text{CH}_4\text{N}_2\text{O})\cdot\text{CaSO}_4$	1.6 times the indicated amount of urea
25 $\text{CH}_4\text{N}_2\text{O}\cdot\text{NaCl}\cdot\text{H}_2\text{O}$	2.3 times the indicated amount of urea.

#### Test Results



The anticariogenic effect of the composition according to the invention has been verified by the following tests.

Initially tests were carried out with the purpose of determining the optimum urea content in a dosage unit of 5 the composition according to the invention.

Dosage units with a urea content of 0, 5, 10, 15, 20, and 30 mg of urea, respectively, were tested by intake immediately after a previous intake of sugar in the form of a sucrose rinse.

10 Telemetric plaque pH measurements were performed on test persons during the period after the sugar rinse as mentioned above, followed by a 10 min. chewing of the tested product according to the invention. The plaque pH measuring continued for 30 min. after this chewing period. The results disclosed that the best effect was obtained by a dosage unit containing 20 mg of urea. Already by 5 mg of urea a clear pH-increasing effect was detected, said effect being significantly better than the effect obtained by compositions free of urea. A urea content beyond 20 mg 20 per dosage unit rendered no further essential advantages.

#### Comparative Tests

Clinical tests have been carried out at the Dental Institute, University of Zürich, Department of Cariology, Periodontology and Preventive Dentistry Bioelectronic 25 Unit, under the leadership of Dr. T. Imfeld. By these tests the following three testing sequences were compared:

- 1) Rinsing for two minutes with a sucrose solution (15 ml, 0.3 mol/l), followed by a monitored period of 30 minutes.
- 30 2) Rinsing with a sucrose solution as used in 1) for two

24

- minutes,  
15 minutes rest period  
10 minutes chewing of a conventional sucrose-free sorbitol-sweetened chewing gum (Gum 31) and then  
5 a monitored period of 30 minutes.  
3) The same testing sequence as for 2) but with a sucrose-free, sorbitol-sweetened chewing gum containing 20 mg urea (Gum 32).

Prior to each testing sequence the test persons chewed a  
10 neutral paraffin for about 3 minutes followed by a resting period of about 15 minutes.

Five persons were tested using the latin square system, each testing sequence being repeated three times for each person.

- 15 The tests were performed as double blind tests.

The telemetric measurement, the plaque pH, was monitored and recorded during the entire testing sequences.

Table I below shows the immediate neutralizing activity during chewing of the two gums expressed by the difference  
20 in plaque pH between the lowest value reached after the sucrose rinse and the highest value reached during subsequent gum chewing, and the prolonged neutralizing effect of the gums expressed by the difference in plaque pH between the lowest value reached after the sucrose rinse  
25 and the lowest value reached during the 30 minutes' monitored period after gum chewing. The result shown in Table I is the average obtained from the 15 testing sequences.

Table I

Immediate neutralizing	Prolonged neutralizing
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25

		activity ( $\Delta$ pH)	effect ( $\Delta$ pH)
	Gum 31	1.81	0.95
	Comparison gum		
5	Gum 32	2.35	1.14
	according to the		
	(i) invention		

The prolonged neutralizing effect can also be expressed on the basis of the square surfaces (pH x minute) obtained from curves where the plaque pH is plotted against the time. The square surfaces limited by the pH-curves above pH 5.7 and a horizontal line at pH 5.7 during the 30 minutes monitored period after chewing of the gums and after a sucrose rinse (testing sequence 1), control) demonstrate the accumulated period above the critical pH 5.7, i.e. on the safe side of the critical level.

On the basis of the same pH-curves the square surfaces (pH x minute) limited by the pH-curves below pH 5.7 and a horizontal line at pH 5.7 during the 30 minutes monitored period after chewing of the gums and after a sucrose rinse (control) gives a combined accumulation of the time and distance below the critical pH 5.7 level, i.e. a combined measure of the caries risk. The average values from 15 testing sequences are shown in Table II:

25 Table II:

	Surface area (pH x min) above pH 5.7	Surface area (pH x min) below pH 5.7
Gum 31	6.85	11.82
30 comparison Gum		

26

Gum 32	14.46	6.64
according to the invention		

Control	0.13	64.73
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5 The following conclusion can be made on the basis of the results shown in Table I and Table II:

- 1) If a test person takes easily fermentable carbohydrates such as sucrose the dental enamel will be exposed to demineralisation for 30-40 minutes.
- 10 2) If a test person with plaque chews sucrose-free chewing gum after intake of easily fermentable carbohydrates an almost instantaneous neutralization occurs (gum 31). During a chewing period of 10 minutes the pH rises to values above the critical pH 5.7, where a remineralisa-  
15 tion occurs. However, it drops below the critical value by the end of the chewing period.
- 20 3) If 20 mg urea have been added to the sucrose-free chewing gum, both an increased instantaneous neutralization and an increased prolongation of the neutralization occur. It appears that pH does not drop below the critical value (5.7) during the chewing period (gum 32).

It can be concluded that a sucrose-free chewing gum having 20 mg urea is far more efficient for neutralizing acidified  
25 plaque layers in humans compared to a sucrose-free chewing gum without urea.

Claims

1. A solid, oral, anticariogenic composition in the form of a chewing gum or a lozenge to be used for neutralizing acid in dental plaque subsequent to eating and drinking,  
5 c h a r a c t e r i s e d in that beyond the conventional chewing gum or lozenge ingredients the composition comprises as active ingredient urea or pharmacologically acceptable substances capable of releasing urea under the conditions prevailing in the oral cavity in an amount from  
10 0.05% by weight to 80% by weight, calculated as urea based on the total weight of the composition, an optional coating not being taken into account.

2. A composition as claimed in claim 1 in dosage unit form, c h a r a c t e r i s e d by each dosage unit  
15 containing at least 5 mg of urea or such an amount of pharmacologically acceptable substances capable of releasing 5 mg of urea under the conditions prevailing in the oral cavity.

3. A composition as claimed in claims 1 to 2,  
20 c h a r a c t e r i s e d by containing 0.2 - 25% by weight of urea.

4. A composition as claimed in claim 1 formulated as a chewing gum, c h a r a c t e r i s e d by being substantially of the following composition:

25	Gum base	15 - 50% by weight
	Sweetener	40 - 80% by weight
	Flavour	0.5 - 4% by weight
	Urea	0.8 - 4% by weight
	Water, colour,	
30	etc.	0 - 5% by weight

an optional coating not being taken into account.

5. A composition as claimed in claim 1 formulated as a lozenge, characterized by substantially containing:

	Sweetener	80 - 99% by weight
5	Flavour	0 - 4% by weight
	Lubricant	0 - 4% by weight
	Urea	0.6 - 4% by weight
	Water, colour, etc.	0 - 4% by weight

10 6. A method for reducing the risks of dental caries subsequent to eating and drinking, characterized  
i s e d by chewing a composition according to claim 1 formulated as a chewing gum immediately after the eating and drinking for a period sufficient for releasing the  
15 active urea ingredient in an amount sufficient for neutralizing plaque acids.

7. A method for reducing the risks of dental caries subsequent to eating and drinking, characterized  
i s e d by sucking a composition according to claim 1  
20 formulated as a lozenge immediately after the eating and drinking for a period sufficient for releasing the active urea ingredient in an amount sufficient for neutralizing plaque acids.

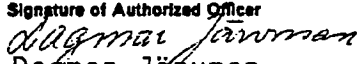
8. A composition substantially as described above and  
25 disclosed in the accompanying specification.

9. A method substantially as described above and disclosed in the accompanying specification.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK86/00050

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC 4		
A 61 K 7/22		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched ?		
Classification System	Classification Symbols	
IPC 4	A 61 K 7/16, /22	
US C1	424:49, 54	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched *		
SE, NO, DK, FI classes as above		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT *</b>		
Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages 12	Relevant to Claim No. 13
X	GB, C, 673 670 (ARTHUR HAROLD STEVENS) 11 June 1952	1-9
X	DE, A, 2 338 177 (BLENDAX-WERKE R. SCHNEIDER & CO) 17 April 1975 & FR, 2238475 US, 3957967 GB, 1483726 CA, 1034505 JP, 50069243	1-9
X	DE, A, 3 011 182 (MÜHLEMANN, HANS R., DR. MED.) 23 October 1980	1-9
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents: 10</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
1986-07-21	1986-07-24	
International Searching Authority	Signature of Authorized Officer	
Swedish Patent Office	 Dagmar Järnman	